MR MONITORING OF THE EFFECT OF ACE2 EXPRESSION ON THE PROTECTION OF THE HEART FROM ISCHEMIC INJURY

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Introduction: Angiotensin converting enzyme 2 (ACE2), a most recent addition to the renin-angiotensin system, has been linked to cardiac dysfunction and hypertension-induced cardiac pathophysiology. In addition, ACE2 expression is up regulated in hearts of human and rats following myocardial infarction. These observations, taken together, led us to propose that an increased ACE2 expression following ischemic injury is a futile attempt by the heart to protect it from damage. This would suggest that cardiac overexpression of ACE2 would exert protective influence following ischemic injury. To address this we used MRI, verified by molecular and histological techniques, to noninvasively follow changes in cardiac function after ischemic injury with and without overexpression of myocardial ACE2.

Experimental: Sprague Dawley rats received 5x10^8 PFU lentiviral particles containing ACE2 cDNA or GFP followed by coronary artery ligation (CAL) of the left anterior descending artery or sham surgery. Cardiac MRI was performed at 24hr and 6wks post CAL at AMRIS as previously described(1,2) Briefly, rats were anesthetized with isoflurane and monitored using the Small Animal Instrument (SAI) monitoring and gating system for respiration rate and cardiac triggering of the MR scanner. On a 4.7T Oxford Magnet using a Bruker Avance Console dorsal and sagittal MR images were acquired using a cardiac-gated gradient echo cineangiographic sequence. Based on these images, 8 short axis views of 2mm thickness and 8-10 frames were prescribed from apex to base. Delayed contrast enhancement (DCE) was performed using gadodiamide (Omniscan [0.5mM/kg]; Amersham Health), IV injected 10 minutes prior to imaging to determine myocardial viability. DCE visually enhances injured portions of the myocardium or areas at risk for infarct(Fig 1A). MRI data was analyzed using CAAS MRV software (Pie Medical Imaging) opensource software from Osirix Medical Imaging (Fig 1A&B).

Results and Discussion: 6wks following CAL there was a 20% decrease in cardiac output (CO), 30% decrease in ejection fraction (EF) and a 57% decrease in LV wall in control rats. Lenti-ACE2 treatment rescued resulted in complete recovery of CO, 60% improvement in EF and 64% improvement in LV anterior (infarcted) wall contractility. Finally, posterior wall motion was decreased by 18% six weeks following CAL and was reversed in lenti-ACE2 treated CAL rats. Volumetric data were analyzed using a 17-segment model (Fig1C) revealing that Lenti-ACE2 treatment also resulted in a 40% improvement LV anterior wall thickness.

Conclusions: MRI was used to demonstrate that cardiac over expression of ACE2 protects the heart from ischemic injury by preserving cardiac functions, LV wall motion and contractility and by attenuating LV wall thinning and infarct.

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